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Mid-term outcomes of percutaneous pulmonary valve replacement with Edwards-Sapien bioprosthesis in native right ventricular outflow tract

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Information on mid-term outcomes of percutaneous pulmonary valve replacement (PPVR) with the Edwards Sapien (ES) valve in the native right ventricular outflow tract (RVOT) are limited. This study assesses mid-term outcomes in 76 patients who underwent PPVR between 2016 and 2022, comparing native (40.8%) and non-native (59.2%) RVOTs. The primary endpoint was a composite of endocarditis, reinterventions, and cardiovascular death and secondary outcomes included prosthetic valve dysfunction (PVD), tricuspid regurgitation (TR), right ventricular ejection fraction (RVEF), and indexed ventricular volumes. The median patient age was 23.9 years. Pulmonary regurgitation was predominant in the native RVOT group (67.7%), while pulmonary stenosis or combined lesions were more common in the non-native group (90.9%). Procedural success was 98.7%. After a median follow-up of 3.3 years, there was no significant difference in freedom from the primary outcome between groups (87.1% native vs. 93.1% non-native, p = 0.875). Endocarditis and reinterventions occurred at 1.2 per 100 patient-years, and PVD at 3.19 per 100 patient-years, with no differences between groups. A 1-year reduction in ventricular volumes and TR was seen only in the non-native group, with no improvement in RVEF. Overall, PPVR with the ES valve demonstrates satisfactory mid-term outcomes in both native and non-native RVOTs.

Keywords Congenital heart disease, Pulmonary valve, Percutaneous pulmonary valve replacement, Edwards Sapien

Abbreviations

CHD	Congenital heart disease
CMRI	Cardiac magnetic resonance imaging
ES	Edwards Sapien
IR	Incidence rate
IRB	Institutional review board

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PPVR	Percutaneous pulmonary valve replacement
PR	Pulmonary regurgitation
PS	Pulmonary stenosis
PVD	Prosthetic valve dysfunction
RVEDVi	Right Ventricle End-Diastolic Volume Index
RVEF	Right ventricle ejection fraction
RVESVi	Right Ventricle End-Systolic Volume Index
RV	Right ventricle
RVOT	Right ventricular outflow tract
ToF	Tetralogy of fallot
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiograph

Right ventricular outflow tract (RVOT) dysfunction such as pulmonary valve stenosis (PS), regurgitation (PR) or mixed lesions may be observed in up to 20% of patients with congenital heart disease (CHD), frequently occurring in patients after repaired Tetralogy of Fallot (ToF)[1]. Recently, it has been associated that pulmonary valve replacement in ToF may improve cardiovascular death[2]

Surgical pulmonary valve replacement has shown low mortality rates and is currently the preferred option in most patients with native RVOT[3], although percutaneous pulmonary valve replacement (PPVR) has evolved in recent years emerging as a minimally invasive alternative for selected patients[4,5].

Balloon-expandable valves are most commonly used for PPVR, with high procedural success and good results in non-native RVOT tracts, namely dysfunctional previously implanted biological valves or conduits[6,7]. The Edwards Sapien (ES) transcatheter valve (Edwards Lifesciences, Irvine, California) has gained popularity due to its greater versatility in terms of sizes and its lower rate of stent rupture and endocarditis when compared PPVR using a Melody TPV® (Medtronic Inc, Minneapolis, Minnesota)[8,9]. These advantages have contributed to expand PPVR to patients with a native RVOT. Recently, self-expandable valves have been developed and appear to be safe and effective for treating patients exclusively with a native tract; however, the experience with this type of valves is still limited, and the Edwards Sapien (ES) valve remains currently the most frequently implanted valve in the native tract[10,11]. Given the paucity of available data, the aim of this study is to evaluate the feasibility of PPVR using ES for native RVOT, to provide mid- and long-term outcomes and to explore right ventricular (RV) remodeling after the intervention comparing with non-native RVOT group.

Methods

Study design and participants

This is an observational, longitudinal, retrospective, and single-center study conducted at a tertiary referral hospital for pediatric and adult patients. All consecutive patients who underwent a first PPVR using the ES valve between May 2016 and October 2022 were included. Patients were classified as native RVOT, which also included previously enlarged tract with surgical patches, or non-native RVOT, including both prior pulmonary bioprostheses or valved conduits (Fig. 1).

Inclusion and exclusion criteria

Among all pulmonary valve replacements performed during the study period, both in pediatric and adult patients, only percutaneous replacements with Edwards Sapiens valves were included. Surgical replacement procedures and hybrid procedures were excluded. Additionally, percutaneous procedures in which the implanted valve was not an Edwards Sapiens were also excluded. The indication for PPVR was established by a heart team comprising CHD specialists, pediatric Cardiology, adult and pediatric cardiac surgeons and invasive cardiologists. Clinical practice guidelines were followed to set the indication for pulmonary valve replacement[5]. Percutaneous pulmonary valve replacement in the native tract was indicated as the first option in pediatrics. However, in adults, it was indicated for patients in need of valve replacement but who were at high surgical risk and had anatomy suitable for the percutaneous approach.

Data collection and follow-up

The electronic health records were reviewed for collecting baseline characteristics, transthoracic echocardiography (TTE) parameters at the time of PPVR and procedural details. TTE images were evaluated by Cardiac Imaging specialists and CHD Cardiologists using current consensus recommendations.

Before the intervention, the current institutional protocol mandates a TTE, cardiac magnetic resonance imaging (CMRI) or computed tomography scan and, when deemed necessary, a pre-operative invasive hemodynamic study including coronary angiography with multiple projections to determine the risk of coronary obstruction when manipulating the RVOT. A clinical follow-up is usually performed at one month, and three months after PPVR, followed by annualy clinical and TEE assessments. Additionally, non-systematic CMRI exams were obtained within 12 months after the procedure. Patients were followed up until death or the last available follow-up, with the last chart review performed for all patients in September 2023.

Outcomes

Procedural success was defined as a successful valve deployment with no more than mild perivalvular leak. Complications occurring during index admission were considered as short-term outcomes. To assess mid- to long-term outcome, we defined a combined primary endpoint consisting of infective endocarditis, need for pulmonary valve reintervention or cardiac death. Infective endocarditis was diagnosed based on the modified

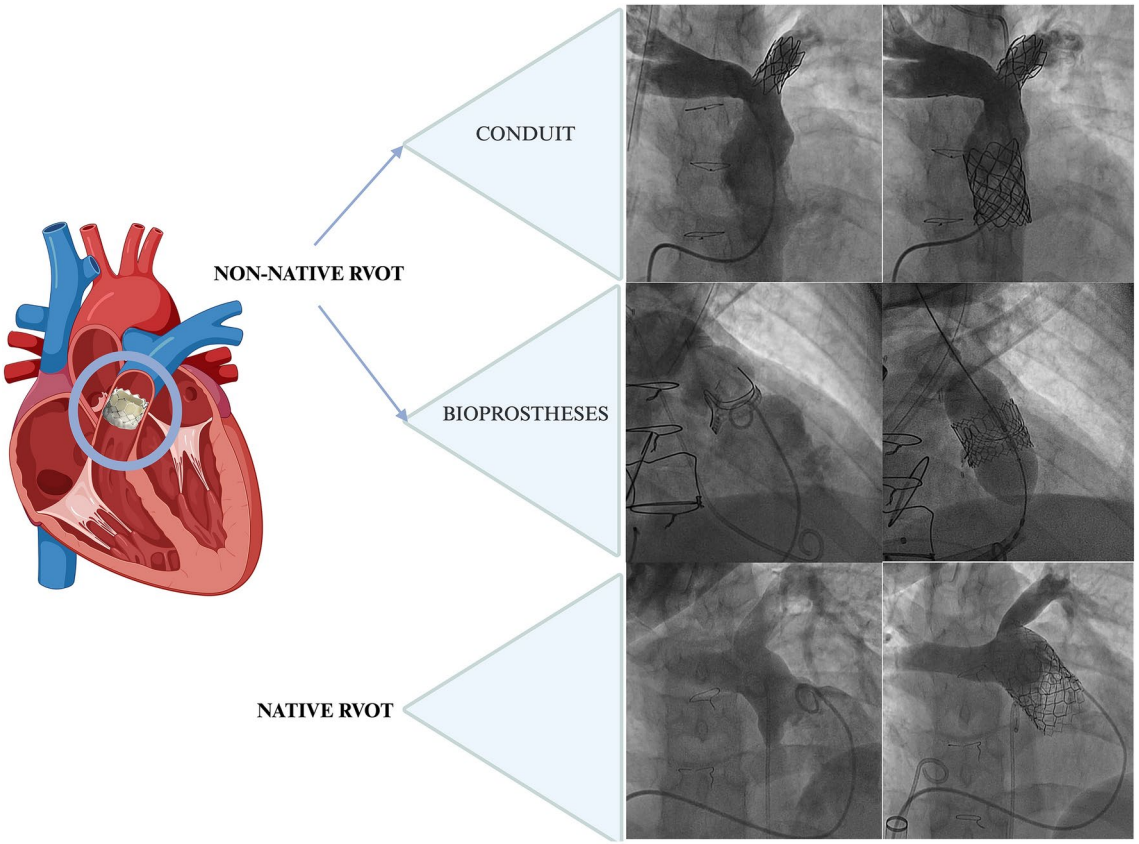

Fig. 1. Anatomical substrates for percutaneous pulmonary valve replacement using the Edwards Sapien bioprosthetic valve.

Duke criteria, considering clinical, microbiological and imaging findings. If the cause of death was unclear from chart review, the family and primary care provider were contacted to gather further information.

Prosthetic valve dysfunction (PVD), tricuspid regurgitation (TR), right ventricular ejection fraction (RVEF), and indexed right ventricular volumes were assessed as secondary outcomes. For this purpose, annual TTE images follow-ups were reviewed, and pulmonary valve dysfunction was defined as PR ≥ moderate or PS with peak gradient ≥ 40 mmHg. The change in TR severity was assessed using TTE and CMRI images were used to assess RVEF, the variation in right ventricle end-diastolic volume index (RVEDVi) and right ventricle end-systolic volume index (RVESVi) after PPVR.

PPVR procedure

PPVR was performed under conscious sedation or general anesthesia with routine biplanar fluoroscopic guidance. Prophylactic antibiotics were administered prior to valve implantation. The preferred access site was typically the femoral vein, although the jugular vein was used in selected cases. To maintain anticoagulation, unfractionated heparin was administered to achieve an activated clotting time of over 250 s. Hemodynamic assessment of pressures was conducted, and standard angiography was performed both before and after valve implantation. If necessary, subsequent selective coronary angiography was conducted during the procedure using a noncompliant balloon inflated with high pressure in the RVOT. Except for valve-in-valve procedures, pre-stenting was routinely performed in all cases, usually at the same time of PPVR. Balloon-expandable covered stents were typically used in conduits, especially in cases considered to be at high risk of rupture and low risk of compromising flow through a pulmonary branch, whereas bare-metal stents are typically used in the native tract. In selected cases with a large native tract, a jailing technique was employed towards one of the pulmonary branches during pre-stenting. Ensuring a clean passage of the guide through the tricuspid valve and proper positioning of a rigid support guide were performed in the distal pulmonary branches. The use of the GORE® Dryseal Flex introducer sheath became widespread starting in June 2019 in the last 46 patients, thus avoiding entrapment of implantation materials in the subvalvular apparatus of the tricuspid valve. The Edwards Sapien valve, available in different sizes (20, 23, 26, 29 mm), was used for delivery using the NovaFlex system for the Sapien XT valve and the Commander delivery system for the Edwards Sapien S3 valves. Valve sizing in non-native RVOT was determined by the size of the existing bioprosthesis or conduit. Intentional ring fracture was performed in selected valve-in-valve cases to achieve a larger inner diameter before implantation. For conduits, the distensibility of different conduit types and the degree of calcification were also considered. In the native RVOT, prior CT imaging and sizing evaluation with semi-compliant catheter balloons up to 28 mm were

essential to assess right ventricular outflow tract compliance, define the landing zone, and confirm the presence of a waist at the implantation site. Rapid pacing was not typically required and was only performed in cases with complex anatomies that required greater control during valve deployment. The procedure could involve predilatation, especially in cases of calcified or tortuous conduits, or degenerated pulmonary bioprostheses, as well as post-dilatation in cases of significant residual gradient or underexpansion of the valve. Figure of eight sutures or closure devices such as the Perclose Proglide TM (Abbot, USA) were used in all cases to achieve venous hemostasis. The Fig. 2 illustrates the steps of PPVR on the native tract.

Statistical analysis

Patients were compared based on whether they belonged to the native RVOT (with or without transannular patches) versus those with bioprosthetic valves or valved conduits. Categorical variables were expressed as counts and percentages and compared using the chi-square test or Fisher's exact test. Continuous variables were presented as medians with interquartile ranges or means with standard deviations. To compare continuous variables, the Student's t-test or Mann–Whitney U test were employed, depending on normality, as assessed by the Shapiro–Wilk test. Kaplan–Meier survival curves were used to graphically represent the combined primary endpoint for each group and statistical significance was tested with the log-rank test. The incidence rates of primary endpoints and PVD were compared between groups. Differences in echocardiographic outcomes and RV remodeling were compared using paired Student's t-test or Wilcoxon signed-rank test, as appropriate. Subsequently, differences between the two groups were compared using independent Student's t-test or Wilcoxon rank-sum test. A two tailed p-value < 0.05 was considered statistically significant for all comparisons. A sensitivity analysis conducted after excluding patients lost to follow-up showed that the main results remained unaltered, with no differences observed in primary outcomes between groups. The statistical analyses were performed using Stata, version 15.1.0 (StataCorp, College Station, TX, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki and received approval from the local Institutional Review Board (IRB) (PR(AG)535/2023, dated 15/12/2023). An informed consent waiver was granted by the IRB due to the retrospective nature of the study.

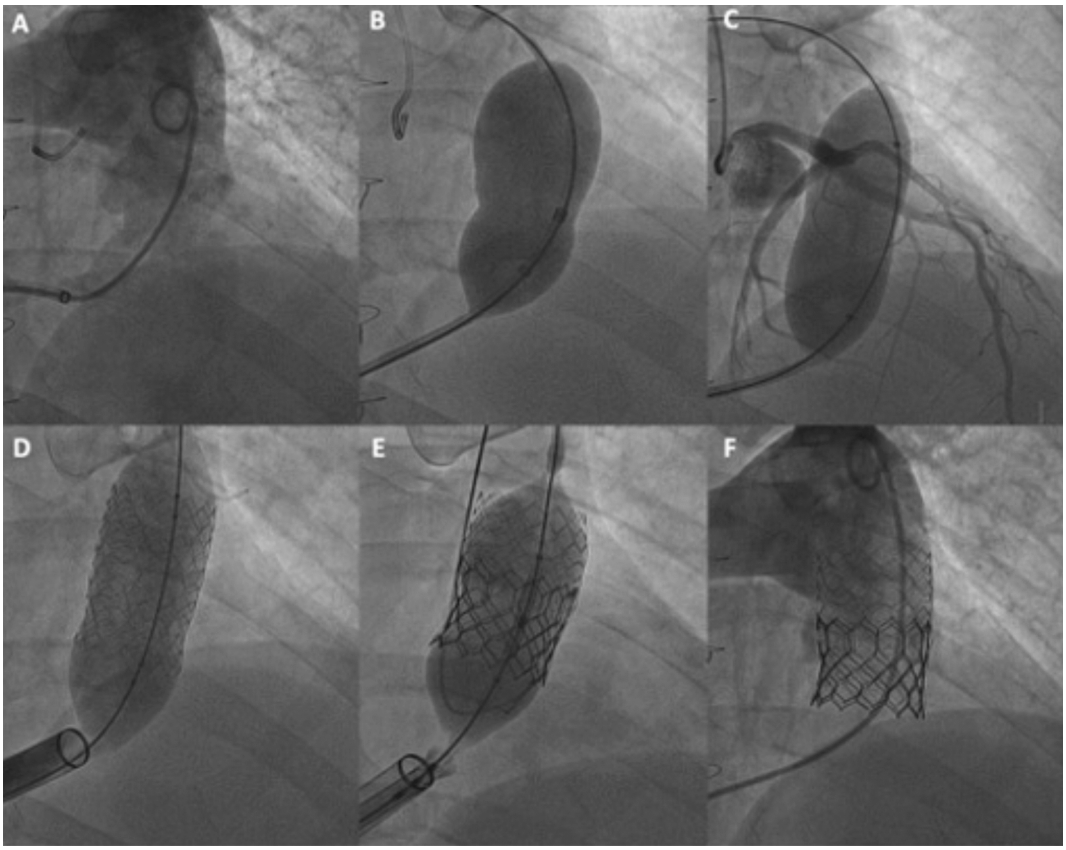

Fig. 2. Percutaneous pulmonary valve replacement. Procedural step-by-step angiography in the native RVOT. (**A**) Angiography showing baseline pulmonary insufficiency (PI), (**B**) Sizing of native RVOT with compliant balloon, (**C**) Sizing with semi-compliant balloon and coronary compression test, (**D**) Prestenting, (**E**) Implantation of a 29 mm Edwards Sapien bioprosthetic valve, (**F**) Final angiography with no residual PI.

Results

Study population and procedural details

During the study period, 76 patients underwent a first PPVR with the Edwards Sapien valve, (Flowchart in **Supplementary Fig. 1**). The median age was 23.9 (15.1–39.7) years old, 31.6% of the patients were women and only 5 (6.6%) weighed less than 30 kg. The most common underlying cardiac conditions were repaired tetralogy of Fallot (43.3%), repaired pulmonary atresia with ventricular septal defect (13.2%) and repaired pulmonary stenosis (15.8%). The primary lesion for which PPVR was indicated was pulmonary regurgitation in 33.3%, pulmonary stenosis in 25.3% and a combination of both in 41.3%. There were 38.2% of patients in NYHA functional class I. Clinical characteristics and echocardiographic findings of the study population are summarized in Table 1.

PPVR was performed on a native RVOT in 31 (40.8%) patients, while it was used on a previous bioprosthesis or conduit in 45 (59.2%). Patients with a native RVOT had a higher degree of pulmonary regurgitation, whereas the non-native RVOT group showed a greater degree of pulmonary stenosis, with higher baseline peak- and RV to right atrium gradients, as well as a lower RV ejection fraction. No differences were observed between the two groups in terms of baseline tricuspid regurgitation severity and RV volumes.

Procedural success was achieved in all patients except in one (98.7%), who had a native RVOT in whom the prosthesis could not be released due to balloon rupture during inflation. Pre-testing and the utilization of a larger valve diameter were more common in the native RVOT group, who also experienced a longer fluoroscopy time and higher radiation exposure. After the procedure, the native RVOT group showed a lower peak-to-peak residual gradient and RV-to-aorta ratio compared to those with a non-native RVOT (Table 2).

		Total (N = 76)	Non-native RVOT (N = 45)	Native RVOT (N = 31)	P value
Age (years)		23.9 (15.1–39.7)	22.6 (15.1–37.1)	28.3 (15.0–51.9)	0.35
Pediatric (< 18 y)		31 (40.8)	17 (37.8)	14 (45.2)	0.52
Female sex		24 (31.6)	16 (35.6)	8 (25.8)	0.37
Body mass index (kg/m2)		22.9 (19.7–25.8)	23.0 (20.3–25.7)	22.8 (18.5–25.8)	0.84
Weight (kg)		60 (51–77)	60 (52–76)	62 (42–77)	0.58
Weight < 30 kg		5 (6.6)	3 (6.7)	2 (6.5)	0.97
CHD	ToF	33 (43.4)	19 (42.2)	14 (45.2)	0.002
	PS	12 (15.8)	4 (8.9)	8 (25.8)	
	PA and VSD	10 (13.2)	8 (17.8)	2 (6.5)	
	TA	5 (6.6)	5 (11.1)	0 (0)	
	Ross procedure	5 (6.6)	5 (11.1)	0 (0)	
	Jatene	4 (5.3)	0 (0)	4 (12.9)	
	Others	7 (9.2)	4 (8.9)	3 (9.6)	
NYHA class	I	29 (38.2)	17 (37.8)	12 (38.7)	0.99
	II	40 (52.6)	24 (53.3)	16 (51.6)	
	III	7 (9.2)	4 (8.9)	3 (9.7)	
ICD or PPM Carrier		9 (11.8)	6 (13.3)	3 (9.7)	0.63
AF or flutter		14 (18.4)	5 (11.1)	9 (29.0)	0.048
2 Sternotomies		51 (67.1)	33 (73.3)	18 (58.1)	0.16
Lesion Type	PS	19 (25.3)	17 (38.6)	2 (6.5)	< 0.001
	PR	25 (33.3)	4 (9.1)	21 (67.7)	
	Both	31 (41.3)	23 (52.3)	8 (25.8)	
LVEF		60 (54–67)	62 (57–66)	60 (53–70)	0.60
Peak to peak gradient		43 (21–65)	58 (38–73)	20 (13–46)	< 0.001
RA-RV gradient		59 (40–70)	65 (52–75)	40 (25–60.)	< 0.001
> moderate-severe TR		18 (23.7)	11 (24.4)	7 (22.5)	0.851
Restrictive RV		25 (33.3)	12 (27.3)	13 (41.9)	0.19
RVEF (%) CMRI		47 (40–58)	42 (34–53)	52 (45–60)	0.020
RVEDVi CMRI		135 (101–166)	136 (100–166)	130 (104–166)	0.85

Table 1. Baseline characteristics of the cohort, based on native or non-native RVOT. Values are median (Q1-Q3) or n (%). AF: Atrial Fibrillation, CHD: Congenital Heart Disease, CMRI: Cardiac Magnetic Resonance Imaging, ICD: Implantable Cardiovascular Defibrillator, LVEF: Left Ventricular Ejection Fraction, PA: Pulmonary Atresia, PPM: Pacemaker, PR: Pulmonary Regurgitation, PS: Pulmonary Stenosis, RVEDVi: Right Ventricular End Diastolic Volume Index, TA: Truncus Arteriosus, ToF: Tetralogy of Fallot, TR: Tricuspid Regurgitation.

		TOTAL (N = 76)	Non-native RVOT (N = 45)	Native RVOT (N = 31)	*P value*
General anesthesia		49 (64.5)	27 (60)	22 (71.0)	0.33
Access	Femoral	74 (97.4)	44 (97.8)	30 (96.8)	0.79
	Jugular	2 (2.6)	1 (2.2)	1 (3.2)	
Coronary compression test		44 (57.9)	18 (40)	26 (83.9)	< 0.001
Prestenting		55 (71.1)	24 (53.3)	31 (100)	< 0.001
Stagged procedure		10 (13.2)	2 (4.4)	8 (25.8)	0.007
Stent type	No stent	21 (27.6)	21 (46.7)	0 (0.0)	< 0.001
	CP 8 Zigs	4 (5.2)	3 (6.7)	1 (3.2)	
	Andrastent	24 (31.6)	5 (11.1)	19 (61.3)	
	Beegraf	7 (9.2)	6 (13.3)	1 (3.2)	
	Optimus	9 (11.8)	9 (20)	0 (0)	
	SINUS XL	9 (11.8)	0 (0)	9 (29.0)	
	EV3	2 (2.6)	1 (2.2)	1 (3.2)	
Covered stent	Yes	20 (26.3)	13 (28.9)	7 (22.6)	< 0.001
	Non covered	35 (46.1)	11 (24.4)	24 (77.4)	
Jailing technique		4 (5.3)	0 (0)	4 (12.9)	0.013
Fracturing		7 (9.3)	7 (15.6)	0 (0.0)	0.021
Dryseal sheath		46 (60.5)	26 (57.8)	20 (64.5)	0.55
Combined pulmonary branch treatment		12 (15.8)	7 (15.6)	5 (16.1)	0.95
Valve type	Sapien XT	24 (31.6)	14 (31.1)	10 (32.3)	0.92
	Sapien S3	52 (68.4)	31 (68.9)	21 (67.7)	
Valve size	20	3 (3.9)	3 (6.7)	0 (0)	< 0.001
	23	28 (36.8)	21 (46.7)	7 (22.6)	
	26	26 (34.2)	21 (46.7)	5 (16.1)	
	29	19 (25)	0 (0)	19 (61.2)	
Invasive peak to peak gradient	Basal	30 (12–41)	36 (28–44)	7.5 (3–29)	< 0.001
	Post	5.5 (2–9)	7 (4–10)	3 (0–9)	0.003
Ratio RV/Aorta (%)	Basal	58 (37–72)	65 (53–73)	35 (25–60)	< 0.001
	Post	31.5 (26–40)	34 (27–41)	29 (25–35)	0.046
Procedure time		180 (153–247)	183 (124–255)	180 (157–231)	0.86
Fluoroscopy time (min)		29 (18–47)	22 (17–41)	37 (26–51)	0.016
X-ray dose (Gy/cm^2)		193 (102–336)	182 (120–320)	194 (92–511)	1.00
Iodinated contrast (ml)		180 (100–243)	157(80–230)	200 (135–250)	0.12
Hospitalization (days)		1 (1–1)	1 (1–1)	1 (1–1)	0.84

Table 2. Procedural features. Values are median (Q1-Q3) or n (%). CP: cheatham platinum, EV3: everflex self-expandable.

Short-term complications

The median hospital length of stay was 1 day in both groups, and a total of 7 periprocedural complications occurred in 6 patients. These included two cases of iatrogenic tricuspid damage, one of which required surgery during follow-up, two cases of pulmonary edema attributed to hyperperfusion following the resolution of pulmonary stenosis that were medically managed, a pulmonary artery bleeding attributed to a lesion caused by the high-support guidewire, a vascular complication that required vascular surgery, an RVOT rupture without hemodynamic compromise, which was successfully sealed percutaneously with a covered stent, and a moderate paravalvular leakage that was corrected percutaneously using a vascular plug. There were no reported cases of coronary compression, device embolization, death, or need for surgical revision (**Supplementary Table 1**).

Follow-up and primary outcomes

Follow-up at 1 year was available for 93.4% of the patients. After a median follow-up of 3.3 years (range 1.8-4.7, with no difference between groups, p = 0,392) and a total of 251 patient-years, two patients had died -one from severe aortic stenosis and the other due to lung disease-, and one patient underwent heart transplantation due to severe left ventricular dysfunction. During the follow-up, there were three cases of endocarditis (one in the native tract and two in the non-native tract) without valve dysfunction. Two were early cases (< 1-year post-implant) caused by organisms including methicillin-sensitive *Staphylococcus aureus* and *Staphylococcus epidermidis*, and one was a late case (> 1 year) attributed to *Cardiobacterium hominis*. All three cases responded well to antibiotic treatment with no need for surgery. Also, there were three redo procedures due to severe valve dysfunction (Fig. 3A). The mechanisms of valve dysfunction in those patients who required reintervention were attributed to one case of thrombosis, another due to a frozen leaflet, and the last one with an unclear cause.

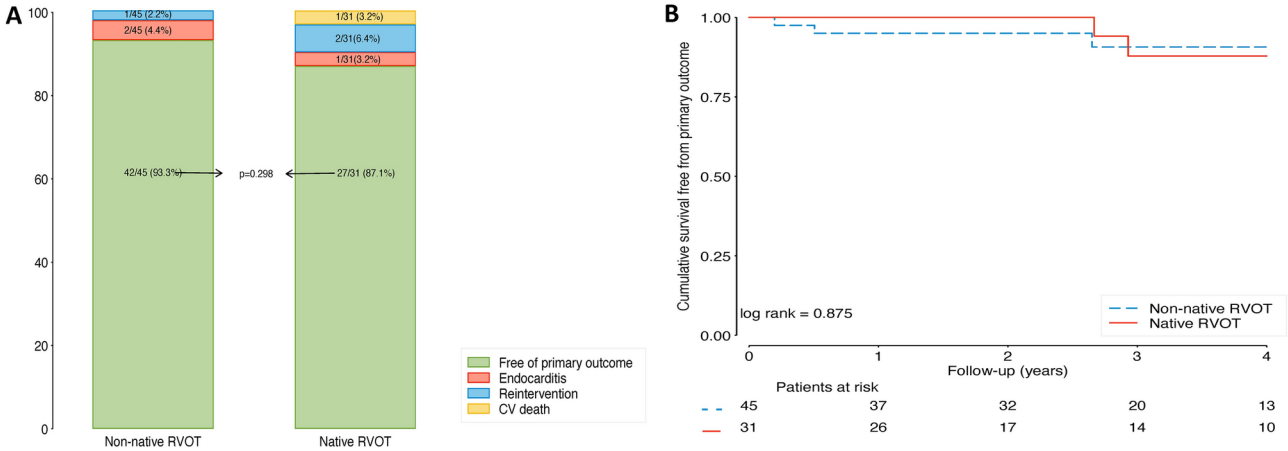

Fig. 3. (**A**) Primary outcome after percutaneous pulmonary valve replacement according on RVOT implantation and (**B**) Kaplan–Meier display showing survival free from primary outcome.

	TOTAL (N = 76), IR	Non-native RVOT (N = 45), IR	Native RVOT (N = 31), IR	CI 95% of IR ratio
Primary end-point	2.79	1.96	4.10	0.35–14.29
CV death	0.40	0	1.02	0.04-
Reintervention	1.20	0.65	2.05	0.16–185.19
Endocarditis	1.20	1.31	1.02	0.01–15.07
PVD	3.18	2.61	4.10	0.29–8.42

Table 3. Incidence rates of the components of the combined primary end-point and prosthetic valve dysfunction (PVD). IR: incidence rate (per 100 person/year).

The incidence rate (IR) of CV death was 0.40 per 100 patient-years and the IRs of infective endocarditis and pulmonary valve reinterventions were both 1.2 per 100 patient-years, with no difference between groups (Table 3). In the native RVOT group, 87.1% remained free from the combined endpoint, compared to 93.1% free from the event in the non-native group (Fig. 3B, log-rank p = 0.875).

Secondary outcomes

PVD occurred in 8 (11.8%) patients during the follow-up (4 in the native RVOT and 4 in the non-native RVOT, p = 0.422). Most cases presented with stenosis or mixed lesions, except for two cases that had pure pulmonary regurgitation (PR), with no difference in the type of substrate treated. Two cases were due to thrombosis, three due to a frozen leaflet, one due to calcification and degeneration of the valve, and etiology was uncertain in the remaining cases (**Supplementary Table 2**). The IR of PVD, was similar between groups, with an overall incidence rate of 3.2 per 100 patient-years (Table 3).

At one-year, we observed a greater than moderate pulmonary regurgitation (PR) in two patients (one in each group; Fig. 4). There were no differences between groups in the maximum pulmonary gradient at one-year, and gradients remained unchanged during the follow-up period (Fig. 4). Regarding RV remodeling, we observed a significant reduction at one year in RV volumes, especially in the non-native RVOT, but no changes in RV ejection fraction. There was a reduction in the rates of moderate to severe TR after PPVR, mostly due to a reduction in the non-native RVOT group (Fig. 5 **and** Table 4). A reduction in NYHA functional class by at least 1 point was noted in 29 (38.2%) patients, with no differences between groups (p = 0.297).

Discussion

The present study shows that patients undergoing PPVR using an ES valve on a native RVOT, when compared to patients undergoing the same procedure on a previous prosthesis or conduit, have similar procedural success rates, an equally low rate of complications in both short- and mid-term follow-up, similar valve function over time and comparable benefits in terms of RV remodeling. However, no benefits in TR reduction were observed in native RVOT compared to those with no native RVOT after PPVR.

Current alternatives to PPVR using ES valves are PPVR using a Melody valve[6,12]or a surgical PVR[13]. However, a registry reporting 10-year outcomes of 150 patients undergoing a Melody valve has shown an exceedingly high rate of need for reintervention (40% at 10 years) and endocarditis (annualized rate of 2%), with endocarditis being the most common cause of death[14]. A meta-analysis comparing both valves found that endocarditis occurred in 4.9% of Melody valves (n = 3616) and only in 1.3% of ES valves (n = 501)[15]. However, a recent multicenter registry challenges this association and reports that factors predisposing to the development of endocarditis

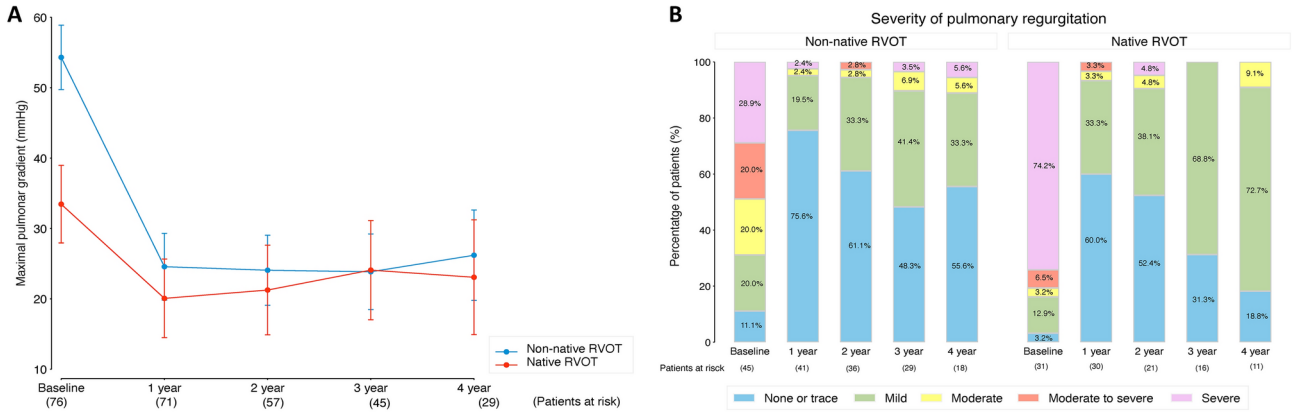

Fig. 4. Valve function over time, based on native or non-native RVOT. (**A**) Degree of pulmonary regurgitation during follow-up. (**B**) maximal pulmonary gradient assessed by transthoracic echocardiography.

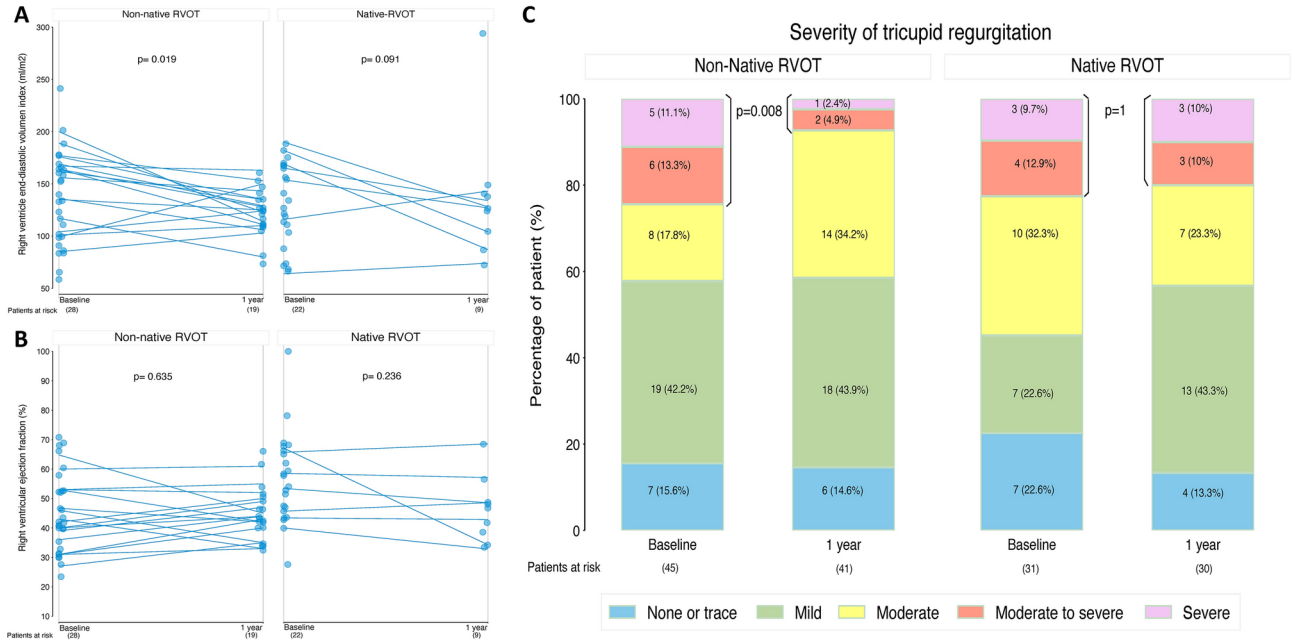

Fig. 5. Right ventricular remodeling after pulmonary valve replacement. (**A**) change in right ventricular end-diastolic volume assessed by cardiac magnetic resonance imaging (CMRI). (**B**) change in right ventricular ejection fraction assessed by CMRI. (**C**) change in tricuspid regurgitation assessed by echocardiography.

were a younger age, a previous history of endocarditis, and a higher residual gradient, but this association was not found based on the type of valve used in PPVR[16].

A meta-analysis showed that surgical PVR is associated with low mortality rates at 30 days (0.9%), 5 years (2.7%), and 10 years (6.2%), and also with low rates of reintervention (3.7% at 5 years and 16.8% at 10 years)[13], so that compared with PPVR using a Melody valve, surgical PVR might reduce costs at 5 years, given the higher rates of complications and reinterventions in the Melody group[17], although these results are debatable[18]. In a study comparing PPVR and surgical PVR in adult patients from the US after 2016, when the ES valves became available, an increase in PPVR was observed, with no difference in in-hospital mortality but lower rates of pacemaker implantation, cardiac arrest, cardiogenic shock, cardiac tamponade, postprocedural respiratory issues, postprocedural bleeding, and blood transfusion in the PPVR group when compared to the surgical PVR[19], suggesting that the utilization of the ES valve for PPVR might change the preferred approach in patients requiring PVR. Thus, demonstrating that the feasibility of PPVR using ES on the native RVOT is paramount to expand the pool of patients that may benefit from this technique.

To date, several studies have reported satisfactory results regarding the safety and success of percutaneous implantation of the ES XT, and ES3 valves in the pulmonary position in patients with conduits and bioprosthetic valves[7,20,21]. More recently, it has been reported that PPVR may also be feasible in patients with native RVOTs[4,22–24]. In this regard, one of the most relevant multicenter registry[4]included 774 patients undergoing PPVR with the

	Total			Non-native RVOT			Native RVOT		
	Basal	1 year	P-valor	Basal	1 year	P-valor	Basal	1 year	P-valor
Peak gradient	43 (21–65)	20 (16–28)	**< 0.001**	58 (38–73)	21 (17–29)	**< 0.001**	20 (13–46)	19 (12–23)	**0.002**
RA-RV gradient	59 (40–70	31 (25–42)	**< 0.001**	65 (52–75)	38 (29–46)	**< 0.001**	40 (25–60)	29 (23–25)	**0.009**
RVEF CMR	47 (40–58)	44 (40–50)	0.909	42 (34–53)	44 (40–50)	0.635	52 (45–60)	46 (40–47)	0.234
RVEDVi	135 (101–166)	126 (108–139)	**0.003**	136 (100–167)	124 (110–135)	**0.019**	130 (104–166)	128 (104–143)	0.091
RVESVi	69 (45–96)	70 (56–83)	**0.010**	72 (53–109)	68 (59–76)	**0.023**	59 (34–83)	72 (34–84)	0.176
PR > moderate	45/71 (63)	2/71 (3)	**< 0.001**	21/41 (51)	1/41 (2)	**< 0.001**	24/30 (80)	1/30 (3)	**< 0.001**
TR > moderate	18/71 (25)	9/71 (13)	**0.012**	11/41 (27)	3/41 (7)	**0.008**	7/30 (23)	6/30 (20)	1.000

Table 4. Secondary endpoints, preprocedural and after 1 year follow-up. Values are median (Q1-Q3) or n (%). PR: Pulmonary Regurgitation, RA: Right Atrium, RV: Right Ventricle, RVEF: Right Ventricular Ejection Fraction, RVEDVi: Right Ventricular End-Diastolic Volume Index, RVESVi: Right Ventricular End-Systolic Volume Index, TR: Tricuspid Regurgitation.

ES valve, of which 397 (51.3%) procedures were performed on native RVOTs with a procedural success rate of 97.4% and a 10% rate of acute complications, with device embolization being the most frequent (4.5%), and only 2 deaths reported during the procedure, with no differences between native and non-native RVOTs. Less than half of the cohort had an available follow-up at one year, and the authors report a 5.5% rate of severe pulmonary regurgitation, 1.7% rate of endocarditis, 4.4% need for reintervention and 1.8% rate of mortality, similar to our results. Similar to other authors' findings, we observed that larger prostheses were frequently implanted in the native RVOT compared to the non-native RVOT, often requiring 29 mm prosthesis, leading to lower gradients. The EUROPULMS3 registry was recently published, comprising 840 patients (50.7% with native or patched RVOT), with a median follow-up of 20.3 months, showing also similar results. It reported a high success rate of 98.5% and a low cumulative incidence at 3 years for infective endocarditis (0.9%), pulmonary valve replacement (1.3%), and pulmonary thrombosis (0.7%). Notably, a lower incidence was observed for larger valves ($P = 0.009$)[24].

We used intentional ring fracture in 7 out of 21 valve-in-valve procedures to enlarge the pulmonary valve orifice, with no differences in gradients compared to those without fracturing. In a study that evaluated this approach, intentional ring fracture successfully enlarged the pulmonary valve orifice in 37 TPVR patients, resulting in improved inner diameter and similar gradients[25].

Longer-term results of PPVR using the ES valve for the native RVOT are scarcer[7,20,26]. The French registry, with a mean follow-up of 4.6 ± 1.8 years, examined the clinical outcomes of 62 patients, including 17 (27%) with native RVOT who underwent the Sapien XT implantation. They found that freedom from valve-related reintervention at 3 and 5 years was 96.6% and 89.0%, respectively, and freedom from infective endocarditis was 98.4% at 5 years[26]. Similar results were obtained in the COMPASSION study, with a freedom from reintervention of 93.7% and freedom from endocarditis of 97.0% at 3 years[7]. In our study, with a median follow-up of 3.3 years, we observed comparable results, with freedom from reintervention in 96.1% and freedom from endocarditis in 96.1%, without observing differences between native and non-native RVOT. We also describe a rate of valve degeneration of 3.2 per 100 patient-years.

In terms of RV remodeling, we observed a reduction in RV volumes, but no change in RV ejection fraction. Although RV dilatation was similar between groups, patients with non-native RVOT had higher gradients and a poorer RV ejection fraction at baseline, but it also remained unchanged after PPVR. These data are in line with those observed after surgical PVR, where a consistent reduction in RV volumes is noted, but RV ejection fraction tends to remain unchanged[27–29]. The reduction in TR severity observed in our cohort (from 25% of patients showing moderate-to-severe TR at baseline to 13% after PPVR, $p = 0.012$) was mostly observed in patients with non-native RVOT. In a study comprising 300 patients undergoing Melody PPVR on a dysfunctional conduit, TR also improved in 65% of the 75 patients with moderate-to-severe TR at baseline[30]. We postulate that the predominant stenotic nature of the lesion in patients with conduits and bioprostheses leads to pressure overload, whereas in native RVOT, volume overload tends to predominate, resulting in greater ring dilatation and less improvement in TR after PPVR.

Limitations

As an observational, single-center retrospective study, limitations must be acknowledged, and causality cannot be inferred from the association observed between procedural and cardiovascular outcomes. Although this is one of the largest single-center reports of PPVR, the sample size remains relatively limited, which precludes subgroup analysis and our results may not be generalizable to all the population. Regarding the data obtained on remodeling, despite the high adherence to echocardiographic follow-up, there is missing data on CMRI images, which could have biased the results. In addition, the indications of PPVR differ in pediatric patients compared to adults, making the mix heterogeneous. On the other hand, 5 (6.6%) of the patients were lost to follow-up,

primarily due to geographic relocation. **Supplementary Table 3** presents the characteristics of patients with complete follow-up compared to those lost to follow-up, showing similar features except for younger age among those lost to follow-up (median age 10.0 vs. 25.5 years, p = 0.021), which may potentially introduce bias into the observed results. However, after excluding patients lost to follow-up, a sensitivity analysis demonstrated that the primary results remained consistent. Finally, we should note that this study does not aim to compare PPVR to surgical PVR, and findings from this registry do not apply to patients undergoing surgical PVR.

Conclusions

Percutaneous pulmonary valve replacement in patients with a native RVOT is feasible with high procedural success rates and comparable low rate of short- and long-term complications, including endocarditis, reintervention or cardiovascular death, to patients with previous prosthesis or conduits.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions
Y. B, G. M, L. D, P. B, F. R, and I. F contributed to the study conception and design. M. C, V. G, B. G, A. P, B. M, and Q. F were involved in patient selection and data collection. E. R, JA. B, I. F, B. G, F. G, and G. G participated in the analysis and interpretation of results. Y. B, G. M, and L. D were responsible for manuscript preparation. All authors critically reviewed the manuscript content, supervised the results, and approved the final version of the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Disclosures statement
Dr. García Del Blanco has served as a proctor for Edwards Lifesciences All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Consent statements
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